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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,448	WEISS ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *14-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004 and 27 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Application, filed April 14, 2004, claims priority to U.S. Provisional Application 60/462,771, filed April 14, 2003 and U.S. Provisional Application, 60/477,991, filed June 6, 2003.

Claims 1-38 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-4 in the reply filed on March 2, 2005 is acknowledged. The traversal is on the ground(s) that Groups I, II, XI, and XV should be examined together as this would not impose a serious burden on the Examiner (Applicant's Response, March 2, 2005, page 13, 3rd parag.). This argument has been found partially persuasive. In addition to Group I, the Examiner will also examine Groups II and III. The Applicant has indicated that a search for a mouse having a null mutation in both alleles of the AHSP gene (Group I) would encompass a search for a mouse having a null mutation in one of the alleles of the AHSP gene (Group II). This has been found convincing. In addition to considering the mice in Groups I and II, the Examiner will examine the first method of use of the mice (Group III). However, the Examiner does not find the argument convincing that the mice in groups XI and XV should also be considered in the examination. This is because the mice in Group XI (mice having a homozygous null mutation in the AHSP gene and a heterozygous null mutation in the beta major and minor globulin gene) are

materially different from the mice in Groups I and II. In addition to the null mutation of AHSP, the mice of Group XI would also need to be examined for the biological effect(s) resulting from the disruption of the beta major and minor globulin gene. This would require additional searches. Similarly, the mice in Group XV (mice having a homozygous null mutation in the AHSP gene and a homozygous null mutation in at least one alpha globulin gene) are materially different from the mice in Groups I and II. In addition to the null mutation of AHSP, the mice of Group XV would need to be examined for the biological effect(s) resulting from the disruption of at least one alpha globulin gene. This would require additional searches. Therefore, the mice in Groups XI and XV will not be considered in this examination.

The Applicant has indicated that Group VIII (claims 23-26, drawn to a method of producing anti-AHSP antibodies and anti-AHSP antibody preparations) has not been set forth how it is related or unrelated to the other Inventions. The Examiner agrees that Group VIII is related to Group I as product and process, as the methods of producing AHSP specific antibodies are carried out in mice which harbor a homozygous null mutation in the AHSP gene. Thus, if claim 1 is found allowable, Group VIII will be rejoined and the claims of Group VIII will be examined on their merits.

The Applicant has also addressed the issue of being unduly and unfairly burdened with excessive fees and costs associated with prosecution and maintenance of eighteen separate patent applications. While this argument has been considered, the argument is not relevant to restriction election practice.

The Examiner maintains that the claims had been properly divided into separate Inventions in the Restriction Requirement, as each invention was patentable distinct and unique.

The requirement is still deemed proper and is therefore made FINAL.

Because the Examiner has combined Groups I-III in this examination, the Groups and the claims they encompass are as follows:

Group I: Claims 1-13, drawn to a mouse harboring a homozygous null mutation in the alpha hemoglobin stability protein (AHSP) gene, a mouse harboring a heterozygous null mutation in the AHSP gene, and a method of screening for therapeutic agents which useful for the treatment and/or prevention of an AHSP related disorder, using the homozygous AHSP null mice.

Group II: Claims 14-16, drawn to a method of diagnosing an AHSP-related disorder in a test subject.

Group III: Claim 17, drawn to a method of screening for compound which modulate the activity of an AHSP polypeptide, wherein the method comprises contacting at least one test compound with the AHSP polypeptide in a reaction medium.

Group IV: Claim 18, drawn to copounds identified by the screening methods of claim 11 or 17.

Group V: Claims 19-22, drawn to a method of treating or ameliorating symptoms of an AHSP-related disorder by overexpressing a nucleic acid encoding AHSP in a patient.

Group VI: Claims 23-26, drawn to a method of producing anti-AHSP antibodies and anti-AHSP antibody preparations.

Group VII: Claim 27, drawn to a kit comprising one or more molecules for the detection of AHSP expression.

Group VIII: Claim 28, drawn to transgenic mice which overexpress AHSP,

Group IX: Claim 29, drawn to a mouse having a homozygous null mutation in the AHSP gene and a heterozygous null mutation in beta major and minor globulin genes.

Group X: Claims 30 and 31, drawn to method for assessing the activity of compounds useful for the treatment and/or prevention of an AHSP-related disorder.

Group XI: Claim 32, drawn to a compound identified by the method of claim 30.

Group XII: Claim 33, drawn to a method of treating or ameliorating symptoms of an AHSP-related disorder by administering the compound of claim 32.

Group XIII: Claim 34, drawn to a mouse having a homozygous null mutation in the AHSP gene and a homozygous null mutation in at least one alpha globulin gene.

Group XIV: Claims 35 and 36, drawn to a method of assessing the activity of compounds useful in the treatment and/or prevention of an AHSP-related disorder using the mice in claim 34.

Group XV: Claim 37, drawn to a compound identified by the method of claim 35.

Group XVI: Claim 38, drawn to a method of treating or ameliorating symptoms of an AHSP-related disorder comprising administering the compound of claim 37 to a patient.

Claims 14-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 2, 2005.

Claims 1-13 are drawn to a mouse comprising a homozygous null mutation of the alpha-hemoglobin stability protein (AHSP) gene, a mouse comprising a heterozygous null mutation in the AHSP gene, and a method of screening for therapeutic agents which affect AHSP, using the mouse comprising homozygous null mutation of the AHSP gene.

Information Disclosure Statement

The information disclosure statement filed August 30, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Shaeffer, et al., 1995 (C20) and dos Santos, et al., 2004 (C21) have not been

considered since copies of these references have not been provided. These references thus, have been crossed off the IDS.

References C13-C17 are GenBank printouts of AHSP sequences from different species of animals. While they have been considered, they have been crossed off the IDS, as no publication date has been provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous null mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin,

2) a transgenic mouse comprising a heterozygous null mutation in its endogenous AHSP gene, wherein the transgenic heterozygous AHSP mouse, compared to a wild type mouse, expresses half the amount of functional AHSP

protein, and wherein the transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene exhibits an elevated reticulocyte count,

4) a method for assessing the activity of a compound useful for the treatment or prevention of AHSP-related anemia, comprising providing at least one transgenic mouse comprising a homozygous mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin and assessing said mouse for an alteration in AHSP activity, administering a test compound to said mouse, wherein administration further comprises determining toxicity of the compound in a control mouse, and assessing said mouse for inhibition of anemia,

does not reasonably provide enablement for:

1) a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene,

wherein there is no expression of functional mouse AHSP protein, wherein there is expression of functional AHSP protein from other species of animal,

wherein a fraction of the transgenic mice comprising a homozygous null mutation are fertile and of those that are fertile, transmit the null mutation to its offspring,

wherein a null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following microinjection of embryonic stem cells into a mouse blastocyst, or wherein null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following co-incubation of embryonic stem cells with a fertilized egg or morula and

wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin,

2) a transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene,

wherein the transgenic heterozygous AHSP mouse, compared to a wild type mouse, expresses half the amount of functional AHSP protein and also expresses a hypomorphic or hypermorphic form of AHSP,

wherein a fraction of the transgenic heterozygous mice are fertile and of those that are fertile, transmit the null mutation to its offspring,

wherein a null mutation has been introduced into any ancestor of the transgenic mice comprising a heterozygous null mutation, following microinjection of embryonic stem cells into a mouse blastocyst, or wherein null mutation has been introduced into an ancestor of the transgenic mice comprising

a heterozygous null mutation, following co-incubation of embryonic stem cells with a fertilized egg or morula, and

wherein the transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene exhibits an elevated reticulocyte count,

3) a method for screening for therapeutic agents which affect AHSP activity, comprising administering a test compound to a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene,

wherein there is no expression of functional mouse AHSP protein, wherein there is expression of functional AHSP protein from other species of animal,

wherein a fraction of the transgenic mice comprising a homozygous null mutation are fertile and of those that are fertile, transmit the null mutation to its offspring,

wherein a null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following microinjection of embryonic stem cells into a mouse blastocyst, or wherein null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following co-incubation of embryonic stem cells with a fertilized egg or morula, and

wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated

morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin,

4) a method for screening for therapeutic agents which affect AHSP activity, comprising administering a test compound to a transgenic mouse comprising a homozygous mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin, and assessing said mouse for an alteration in AHSP activity,

5) a method for assessing the activity of a compound useful for the treatment or prevention of AHSP-related anemia, comprising providing at least one transgenic mouse comprising a homozygous mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin and assessing said mouse for an alteration in AHSP activity, administering a test compound to said mouse, wherein administration further comprises determining

toxicity of the compound in a control mouse, and assessing said mouse for inhibition of any AHSP-related disorder (comprising a-thalassemia, b-thalassemia, spongiforma encephalopathy, prion disease, and Alzheimer's disease) other than anemia.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant invention is drawn to a mouse comprising a homozygous null mutation of the alpha-hemoglobin stability protein (AHSP) gene, a mouse comprising a heterozygous null mutation in the AHSP gene, and a method of screening for therapeutic agents which affect AHSP, using the mouse comprising homozygous null mutation of the AHSP gene.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the

quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

According to claim 1, the transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, appears to be comprised of at least one additional transgene. An additional transgene seems to be implied, as claim 1 specifically points out that the transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene a does not express mouse AHSP. However, at the time of filing, the specification does not teach an artisan how to make and use a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein said mouse is further comprised of a transgene comprising a nucleic acid sequence encoding another animal species of AHSP, other than mouse, operably linked to a promoter. An artisan cannot envision all possible transgenic mice this would encompass, as one variable to consider is the promoter. While the specification teaches that AHSP has a role in blood, the specification does not teach an artisan of other possible roles that AHSP has in other tissues. An artisan cannot envision all possible tissues and phenotypes that would be

encompassed by these mice. For this reason, the specification does not enable an artisan to use the claimed mice for its full breadth.

The implication of claim 2 is that the transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, also exhibits a sterility phenotype and also, of the mice that are fertile, some do not transmit the null mutation to its offspring. This means that the transgenic mice comprising a homozygous disruption in AHSP, in claim 1 are comprised of transgenic mice that are infertile and transgenic mice, while fertile, do not necessarily transmit the null mutation to its offspring. At the time of filing, the specification does not teach an artisan how to use infertile mice and fertile mice that do not transmit the null mutation to its offspring. Thus, the claims are not enabled for its full breadth.

Claims 3 and 4 are to a transgenic mouse of claim 1, wherein said null mutation has been introduced into any ancestor of the mouse comprising a homozygous null AHSP mutation, either at an embryonic stage following microinjection of embryonic stem cells into a mouse blastocyst or comprising a homozygous null AHSP mutation, or at an embryonic stage following co-incubation of embryonic stem cells with a fertilized egg or morula. After 10 generations of breeding, the 10^{th} generation of mouse has 9 generations of ancestor mice. While the founder mouse may have been made either at an embryonic stage following microinjection of embryonic stem cells into a mouse blastocyst or comprising a homozygous null AHSP mutation, or at an embryonic stage following co-incubation of embryonic stem cells with a fertilized egg or

morula, not all of the ancestor mice in the line were produced by microinjection of an ES cell into a blastocyst or by co-incubation of an ES cell with a fertilized egg or morula. Claims 3 and 4, as filed, do not provide guidance as to how one would obtain a transgenic mouse comprising a null ASPH mutation, such that all of its ancestors were made either by microinjection of an embryonic stem cell into a mouse blastocyst or by co-incubation of embryonic stem cells with a fertilized egg or morula

Claims 3 and 4 are to a transgenic mouse comprising a homozygous null AHSP mutation, wherein a null mutation has been introduced following microinjection of embryonic stem cells into a mouse blastocyst or wherein a null mutation has been introduced following co-incubation of embryonic stem cells with a fertilized egg or morula. Claims 3 and 4 read as though following either microinjection of embryonic stem cells into a mouse blastocyst, or co-incubation of embryonic stem cells with a fertilized egg of morula, a null mutation, specific for AHSP disruption had been introduced. However, no guidance by the art or the specification was provided as to how one would obtain transgenic mice comprising a null mutation in AHSP merely by introducing an embryonic stem cell to a mouse blastocyst or by incubating embryonic stem cells with a fertilized egg or morula.

Claim 5 is to a transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene, wherein said mouse exhibits AHSP haploinsufficiency and has an elevated reticulocyte count. Claim 5, as filed, encompasses transgenic heterozygous AHSP disrupted mice, wherein the

disruption of AHSP resulted in a hypermorphic or hypomorphic form of AHSP. This means that these hypermorphic or hypomorphic forms of AHSP are partially functional. However, the specification at the time of filing, does not teach an artisan how to identify and use transgenic heterozygous AHSP disrupted mice comprising a hypermorphic or hypomorphic form of AHSP.

The implication of claim 6 is that the transgenic mouse comprising a heterozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, also exhibits a sterility phenotype and also, of the mice that are fertile, some do not transmit the null mutation to its offspring. This means that the transgenic mice comprising a heterozygous disruption in AHSP, in claim 5 are comprised of transgenic mice that are infertile and transgenic mice, while fertile, do not necessarily transmit the null mutation to its offspring. At the time of filing, the specification does not teach an artisan how to use infertile mice and fertile mice that do not transmit the null mutation to its offspring. Thus, the claims are not enabled for its full breadth.

Claims 7 and 8 are to a transgenic mouse of claim 5, wherein said null mutation has been introduced into any ancestor of the mouse comprising a heterozygous null AHSP mutation, either at an embryonic stage following microinjection of embryonic stem cells into a mouse blastocyst or comprising a homozygous null AHSP mutation, or at an embryonic stage following co-incubation of embryonic stem cells with a fertilized egg or morula. After 10 generations of breeding, the 10^{th} generation of mouse has 9 generations of ancestor mice. While the founder mouse may have been made either at an

embryonic stage following microinjection of embryonic stem cells into a mouse blastocyst or comprising a homozygous null AHSP mutation, or at an embryonic stage following co-incubation of embryonic stem cells with a fertilized egg or morula, not all of the ancestor mice in the line were produced by microinjection of an ES cell into a blastocyst or by co-incubation of an ES cell with a fertilized egg or morula. Claims 7 and 8, as filed, do not provide guidance as to how one would obtain a transgenic mouse comprising a null ASPH mutation, such that all of its ancestors were made either by microinjection of an embryonic stem cell into a mouse blastocyst or by co-incubation of embryonic stem cells with a fertilized egg or morula.

Claims 7 and 8 are to a transgenic mouse comprising a heterozygous null AHSP mutation, wherein a null mutation has been introduced following microinjection of embryonic stem cells into a mouse blastocyst or wherein a null mutation has been introduced following co-incubation of embryonic stem cells with a fertilized egg or morula. Claims 7 and 8 read as though following either microinjection of embryonic stem cells into a mouse blastocyst, or co-incubation of embryonic stem cells with a fertilized egg of morula, a null mutation, specific for AHSP disruption had been introduced. However, no guidance by the art or the specification was provided as to how one would obtain transgenic mice comprising a null mutation in AHSP merely by introducing an embryonic stem cell to a mouse blastocyst or by incubating embryonic stem cells with a fertilized egg or morula.

Claim 9 is to a method for screening for therapeutic agents which affect AHSP activity, comprising administering a test compound to a transgenic mouse comprising a homozygous null mutation of AHSP, and assessing said mouse for an alteration in AHSP activity. The mouse used in the assay is a transgenic mouse comprising a homozygous null mutation of AHSP, wherein the mouse does not produce any functional AHSP protein. As there is no AHSP protein produce by the mouse, an artisan does not know how to carry out a method for screening for therapeutics that affect AHSP using a transgenic mouse comprising a homozygous null mutation of AHSP.

The instant invention of claims 11-13 is drawn to a method for assessing the activity of a compound useful for the treatment and/or prevention of any AHSP-related disorder, wherein the disorders are selected from the group consisting of α-thalassemia, β-thalassemia, spongiform encephalopathy, prion disease, and Alzheimer's disease. The specification at the time of filing teaches an artisan that the phenotypes exhibited by the AHSP homozygous null mouse are a 3-fold increase in reticulocyte counts (specification, page 48, line 22) and anemia (specification, page 54, lines 9-11), and that erythrocytes obtained from AHSP homozygous null mice exhibit an abnormal spiculated morphology (specification, page 48, line 24), denatured hemoglobin inclusions (Heinz bodies) (specification, page 48, line 29), accumulation of precipitated α-hemoglobin (specification , page 48, line 35), a reduced life span (specification, page 50, line 18), and an increased production of reactive oxygen species (ROS) (specification, page 50, line 21). While the specification teaches an artisan these

characteristics that could be used to monitor the effects of a candidate compound on an AHSP homozygous null mouse, the specification does not teach how to monitor the effects of a candidate compound on mouse that exhibits the diseases consisting of α-thalassemia, β-thalassemia, spongiform encephalopathy, prion disease, and Alzheimer's disease.

While the specification teaches that there is a relationship between AHSP and α-thalassemia and AHSP and β-thalassemia, in that the loss of AHSP exacerbates the phenotype resulting from disruption in the α-thalassemia and β-thalassemia genes, the specification does not teach that ASHP causes the phenotype in α-thalassemia and β-thalassemia mice (specification, pages 67-69; applicant particularly points out that AHSP loss exacerbates the phenotype of β-thalassemia on page 67, lines 29-30 and that AHSP loss exacerbates the phenotype of α-thalassemia on page 69, lines 2-3). The art teaches that free α-hemoglobin is highly unstable in cells, and form inclusion bodies (Kihm, et al., page 761, 1st col., 3rd parag. lines 2-4). AHSP was shown to bind and form a stable complex with α-hemoglobin (Kihm, page 761, 1st col., 1st parag. lines 3-4). Further, AHSP bound to α-hemoglobin blocked oxidant-induced α-hemoglobin precipitation Kihm, page 761, 1st col., 3rd parag., lines 16-19). Kihm et al. also teach that when the α-hemoglobin-AHSP complex was incubated with β-hemoglobin, the AHSP-α-hemaglobin complex was disrupted and the α-hemoglobin-β-hemaglobin complex was formed. While the art teaches that AHSP acts as a chaperone, minimizing the presence of free α-hemoglobin,

neither the art nor the specification teach that AHSP has a role in mediating the expression levels of α-hemoglobin or β-hemoglobin. α-thalassemia results from loss of expression of functional a-hemoglobin; β-thalassemia results from the loss of expression of function β-hemoglobin. However, neither the art nor the specification teaches that the loss of AHSP is what causes the loss of α- or β-hemoglobin expression, leading to thalasseima. The specification does not provide guidance as to how an artisan would use a transgenic mouse comprising a homozygous null AHSP mutation in a method for assessing the activity of a compound useful for the treatment of α- or β-thalassemia, as neither the specification nor the art teach that the transgenic mouse comprising a homozygous null AHSP mutation develops α- or β-thalassemia. For this reason, an artisan is not enabled for a method of assessing the activity of a compound in a transgenic mouse comprising a homozygous null AHSP mutation, in an assessment for the inhibition of α-thalassemia or β-thalassemia.

The specification and the art (Miele, et al. 2001, Nature Medicine, 7: 361-364, see IDS) teach that transmittable spongiform encephalopathies (TSE) reduce EDRF (former acryonym of ASHP) transcription levels in cells of the erythroid lineage, neither the art nor the specification teach that ASHP causes the phenotype in TSE mice. For example, the pathological effects of TSE and prion disease are localized to the central nervous system, and the characteristics of TSE and prion disease include vacuolation, gliosis, accumulation of a protease-resistant, abnormally folded isoform of the prion protein, and neuronal cell death (see Miele, et al., 2001, Nature Medicine, 7: 361-364, abstract, see

IDS). However, the specification does not teach that when the AHSP gene was disrupted, that the homozygous and/or heterozygous AHSP disrupted mice exhibited any of these symptoms. An artisan cannot predict without guidance how to treat TSE and prion disease, caused by disruption of AHSP, if no guidance was provided as to how disruption of AHSP leads to the progression of TSE and prion disease. Further, because the specification does not teach that the AHSP mice are comprised of any TSE or prion symptoms, an artisan does not know how to identify any compounds which could be used to ameliorate symptoms of TSE or prion disease. As no guidance was provided as to how loss of AHSP leads to TSE or prion disease, and the specification does not provide guidance as to how an artisan would monitor TSE or prion disease, it would be undue experimentation for an artisan to screen for compounds that would ameliorate the symptoms of TSE or prion disease, which arise as a result of AHSP disruption.

In the case of Alzheimer's disease, the specification provides no guidance as to how the loss of ASHP contributes to the pathology of Alzheimer's disease. The art teaches that the critical features of Alzheimer's disease are that the cerebral cortex is peppered with neurofibrillary tangles and senile plaques (Munoz and Feldman, 2000, CMAJ, 162: 65-72, page 65, under "Structural abnormalities," lines3-5). Munoz and Feldman teach that neurofibrillary tangles consist of aberrantly phosphorylated fibrillary proteins aggregated within the neuronal cytoplasm. Their presence signifies the failure of the neuron to properly maintain its cytoskeleton (Munoz and Feldman, page 66, 1st col., 1st parag.).

With regards to senile plaques, the plaques consist of extracellular deposits of anyloid material and are associated with swollen, distorted neuronal processes called dystrophic neurites (Munoz and Feldman, page 66, 2nd col., 1st parag. under "Senile Plaques"). While the art teaches these embodiments of Alzheimer's disease, the specification does not provide guidance that the transgenic mouse comprising a homozygous null mutation of AHSP exhibits symptoms of Alzheimer's disease. As such, because the specification does not teach these symptoms, an artisan does not know how to monitor inhibition of Alzheimer's disease using the transgenic mouse comprising a homozygous null mutation of AHSP. Thus, the specification does not provide guidance to the artisan for the full scope of the claims.

The specification, while being enabling for:

1) a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous null mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin,

2) a transgenic mouse comprising a heterozygous null mutation in its endogenous AHSP gene, wherein the transgenic heterozygous AHSP mouse,

compared to a wild type mouse, expresses half the amount of functional AHSP protein, and wherein the transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene exhibits an elevated reticulocyte count,

3) a method for screening for therapeutic agents which affect AHSP activity, comprising administering a test compound to a transgenic mouse comprising a homozygous mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin, and assessing said mouse for an alteration in AHSP activity,

4) a method for assessing the activity of a compound useful for the treatment or prevention of AHSP-related anemia, comprising providing at least one transgenic mouse comprising a homozygous mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin and assessing said mouse for an alteration in AHSP activity, administering a test

compound to said mouse, wherein administration further comprises determining toxicity of the compound in a control mouse, and assessing said mouse for inhibition of anemia,

does not reasonably provide enablement for:

1) a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene,

wherein there is no expression of functional mouse AHSP protein, wherein there is expression of functional AHSP protein from other species of animal,

wherein a fraction of the transgenic mice comprising a homozygous null mutation are fertile and of those that are fertile, transmit the null mutation to its offspring,

wherein a null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following microinjection of embryonic stem cells into a mouse blastocyst, or wherein null mutation has been introduced into an ancestor of the transgenic mice comprising a homozygous null mutation, following co-incubation of embryonic stem cells with a fertilized egg or morula and

wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin,

2) a transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene,

wherein the transgenic heterozygous AHSP mouse, compared to a wild type mouse, expresses half the amount of functional AHSP protein and also expresses a hypomorphic or hypermorphic form of AHSP,

wherein a fraction of the transgenic heterozygous mice are fertile and of those that are fertile, transmit the null mutation to its offspring,

wherein a null mutation has been introduced into any ancestor of the transgenic mice comprising a heterozygous null mutation, following microinjection of embryonic stem cells into a mouse blastocyst, or wherein null mutation has been introduced into any ancestor of the transgenic mice comprising a heterozygous null mutation, following co-incubation of embryonic stem cells with a fertilized egg or morula, and

wherein the transgenic mouse comprising a heterozygous mutation in its endogenous AHSP gene exhibits an elevated reticulocyte count,

3) a method for screening for therapeutic agents which affect AHSP activity, comprising administering a test compound to a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene,

wherein there is no expression of functional mouse AHSP protein, wherein there is expression of functional AHSP protein from other species of animal,

wherein a fraction of the transgenic mice comprising a homozygous null mutation are fertile and of those that are fertile, transmit the null mutation to its offspring,

wherein a null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following microinjection of embryonic stem cells into a mouse blastocyst, or wherein null mutation has been introduced into any ancestor of the transgenic mice comprising a homozygous null mutation, following co-incubation of embryonic stem cells with a fertilized egg or morula, and

wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin,

4) a method for assessing the activity of a compound useful for the treatment or prevention of AHSP-related anemia, comprising providing at least one transgenic mouse comprising a homozygous mutation in its endogenous alpha hemoglobin stabilizing protein (AHSP) gene, wherein there is no expression of functional AHSP protein, and wherein the erythrocytes obtained from a transgenic mouse comprising a homozygous mutation in its endogenous AHSP gene exhibits one or more characteristics selected from the group consisting of an abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin and

assessing said mouse for an alteration in AHSP activity, administering a test compound to said mouse, wherein administration further comprises determining toxicity of the compound in a control mouse, and assessing said mouse for inhibition of any AHSP-related disorder (comprising a-thalassemia, b-thalassemia, spongiforma encephalopathy, prion disease, and Alzheimer's disease), other than anemia.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (from which claims 2-13 depend) uses the word, "harboring" to describe the null mutation. Use of this word is imprecise. The Merriam-Webster online dictionary defines "harboring" as:

1 a : to give shelter or refuge to **b :** to be the home or habitat of <the ledges still *harbor* rattlesnakes>; *broadly* **:** CONTAIN 2
2 : to hold especially persistently in the mind **:** CHERISH <*harbored* a grudge>
intransitive senses
1 : to take shelter in or as if in a harbor
2 : LIVE.

Use of the word, "comprising" would render the claim more accurate.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Kihm, et al. (2002, Nature, 417: 758-763, see IDS).

The instant invention is drawn to a mouse comprising a homozygous null mutation of the alpha-hemoglobin stability protein (AHSP) gene, a mouse comprising a heterozygous null mutation in the AHSP gene, and a method of screening for therapeutic agents which affect AHSP, using the mouse comprising homozygous null mutation of the AHSP gene.

Claims 1-4 are to a transgenic mouse comprising a homozygous null mutation in its endogenous alpha hemoglobin stability protein (AHSP) gene, wherein said mouse does not express functional AHSP protein and erthryocytes obtained from said mouse exhibit one or more characteristics selected from the group consisting of abnormal spiculated morphology, reduced life span, increased production of reactive oxygen speices (ROS), and precipitated hemoglobin. Claims 5-8 are to a transgenic mouse comprising a heterozygous null mutation in its endogenous AHSP gene, wherein said mouse exhibits AHSP haploinsufficiency and has an elevated reticulocyte count.

Kihm et al. teach how to make mice comprising a deletion wherein the entire protein-coding region of the AHSP gene was deleted (Kihm et al., page 761, 2nd col., 3rd parag., lines 1-3, see also supplement Figure 1). Kihm et al. teach that AHSP-/- mice exhibited elevated reticulocyte counts, indicative of a

shortened erythrocyte half-life (Kihm, et al., page 761, 2nd col., 3rd parag.). Erythrocytes from AHSP-/- mice exhibited abnormal spiculated morphology and contained denatured hemoglobin inclusions (Heinz bodies) (Kihm, et al., page 761, 2nd col., 3rd parag.). Kihm et al. conclude that the erythrocyte abnormalities in AHSP homozygous null mice resulted from a pathological accumulation of precipitated α-hemoglobin (Kihm, et al., page 761, 2nd col., 3rd parag.).

Kihm et al. also teach that reticulocyte counts from AHSP+/- mice were assessed and determined to be mildly elevated, suggesting that the AHSP haploisufficiency might produce a subtle erythroid phenotype (Kihm, et al. page 762, 1st col., 1st parag.).

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). While the Supplementary Information provided with the Kihm et al. reference teach how to make the targeting construct used in generating AHSP null mice, the Supplementary Information does not

provide explicit information regarding whether the mice were generated by microinjection of embryonic stem cell into a mouse blastocyst (claims 3 and 7) or by introducing embryonic stem cells with a fertilized egg or morula (claims 4 and 8). Despite Kihm et al. not teaching which method was used, an artisan at the time of filing knows that these are two common techniques used to generate knockout mouse. For reasons of inherency, Kihm et al. anticipates the AHSP null mice of the claimed invention, regardless how they were made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kihm, et al., (2002, Nature, 417:758-763, see IDS) in view of Capecchi (1989, TIG, 5: 70-76).

The instant invention is drawn to a mouse comprising a homozygous null mutation of the alpha-hemoglobin stability protein (AHSP) gene, a mouse comprising a heterozygous null mutation in the AHSP gene, and a method of screening for therapeutic agents which affect AHSP, using the mouse comprising homozygous null mutation of the AHSP gene.

Claims 9-10 are to a method for screening for therapeutic agents which affect AHSP activity, wherein the activity is selected from the group consisting of hemoglobin binding and α-hemoglobin synthesis, comprising administering a test compound to a transgenic mouse comprising a null mutation in its endogenous AHSP gene, wherein the mouse exhibits one or more characteristics selected from the group consisting of abnormal spiculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin. Claims 11-13 are to a method for assessing the activity of a compound useful for the treatment and/or prevention of an AHSP related disorder, wherein the disorder is selected from the group consisting of α-thalassemia, β-thalassemia, anemia, spongiform, encephalopathy, prion disease, and Alzheimer's disease, comprising administering a test compound to a transgenic mouse comprising a null mutation in its endogenous AHSP gene, wherein the mouse exhibits one or more characteristics selected from the group consisting of abnormal spiculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin and assessing said mouse for inhibition of said AHSP related disorder. The method further comprises administration of a test compound to a control mouse, to assess toxicity of said test compound.

Kihm et al. teach how to make mice comprising a deletion wherein the entire protein-coding region of the AHSP gene was deleted. Kihm et al. teach that AHSP-/- mice exhibited elevated reticulocyte counts, indicative of a shortened erythrocyte half-life. Erythrocytes from AHSP-/- mice exhibited

abnormal spiculated morphology and contained denatured hemoglobin inclusions (Heinz bodies). Kihm et al. conclude that the erythrocyte abnormalities in AHSP homozygous null mice resulted from a pathological accumulation of precipitated α-hemoglobin (Kihm, et al., page 761, 2nd col., 3rd parag.).

Kihm et al. also teach that reticulocyte counts from AHSP+/- mice were assessed and determined to be mildly elevated, suggesting that the AHSP haploisufficiency might produce a subtle erythroid phenotype (Kihm, et al. page 762, 1st col., 1st parag.).

While Kihm et al. do not teach a method wherein the AHSP homozygous null mice were used in a screen to identify compounds that could be used in treatment, therapy, or prevention of an disorder caused by AHSP disruption, Capecchi teaches that a mouse comprising a homozygous null mutation in a gene of interest and exhibiting a phenotype aremouse models for human genetic diseases. Such models should prove useful for analyzing the pathology of the disease as well as providing systems for exploration of new therapeutic protocols, including gene therapy (Capecchi, page 76, 1st col., 2nd parag.) This is further supported by Kihm et al. who teach that delivery of AHSP or functional analogues are predicted to decrease ineffective erythropoiesis caused by the precipitation of α-hemoglobin in β-thalassamia (Khim et al., page 762, 1st col., 3rd parag. to 2nd col.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the AHSP homozygous null mice in a method for screening for agents which have therapeutic effect

and/or can be used in a treatment or prevention of a disorder caused by AHSP disruption.

One having ordinary skill in the art would have been motivated to use the AHSP homozygous null mice in a screen for therapeutic agents in order to obtain therapeutic agents that may treat or prevent a condition caused by AHSP disruption.

There would have been a reasonable expectation of success given that using a mouse model of disease in a screen for medicaments is well known in the art. Further, Khim et al. teach that AHSP and functional analogues of AHSP can be used to decrease ineffective erythropoiesis cause by precipitation of α-hemoglobin.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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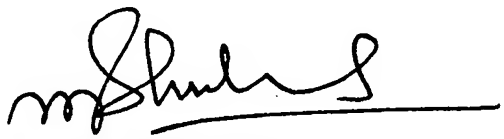

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